

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:

Meng YANG et al.

Application No.: 10/714,068

Filed: November 14, 2003

For: WHOLE-BODY OPTICAL IMAGING OF  
GENE EXPRESSION AND USES THEREOF

Confirmation No.: 2630

Art Unit: 1636

Examiner: Celine X. Qian, Ph. D.

**DECLARATION OF ROBERT M. HOFFMAN**

Commissioner for Patents  
P.O. Box 1450  
Alexandria, VA 22313-1450

Dear Sir:

I, ROBERT M. HOFFMAN, declare as follows:

1. I am a Professor in the Department of Surgery at the University of California San Diego Medical Center and am Chairman of the Board and Chief Executive Officer of AntiCancer, Inc., the assignee herein. I have been engaged in diagnostics and laboratory models employing fluorescent protein expression for at least the past 10 years. I obtained my Ph.D. in biology from Harvard University in 1971 and have been practicing in the field of cancer research since that time. I have held academic positions at Harvard Medical School and at the Weizmann Institute and have published about 400 articles on subjects related to cancer and metastasis. I am on the editorial

boards of *AntiCancer Research*, of *Clinical Cancer Research* and of *In Vitro Cellular and Developmental Biology*. A copy of my *curriculum vitae* is attached as Exhibit A.

2. I have reviewed the patent application captioned above and the Office action mailed 25 June 2007, in particular the basis for rejection of claims 39 and 40 under 35 U.S.C. § 112, first paragraph. The Office asserts that these claims lack enablement because observing the presence, absence or intensity of fluorescence of a protein encoded by a nucleotide sequence operably linked to a promoter would not reliably reflect the interaction of a test compound with the promoter. The Office asserts this is in view of complicating factors such as “drug interaction and metabolism.” While it is not entirely clear what is meant by “drug interaction and metabolism” in this context, it is perhaps explained by an earlier statement referred to, that the “intensity of the fluorophore may be the result of interaction with another gene product.”

3. From my experience in dealing with animal models involving fluorescent proteins as indicators, I believe that the occurrence of such interaction would be extremely rare, if existent at all, since I am aware of no mechanism whereby the fluorescence of such proteins is interfered with by other metabolites. Fluorescent proteins have been used as reporters for many years. Nevertheless, should this be of concern, the practitioner could readily control for such an occurrence in a very straightforward manner as follows:

4. A straightforward control would be to place the fluorescent protein-encoding sequence under control of a housekeeping promoter whose ability to control expression is known not to be affected by the test compound used. If indeed the effect of the test compound is only on the promoter being targeted, the level of fluorescence of the control would be identical in both the presence and absence of the test compound. If, for some reason, there is an impact of the compound

on some other metabolite which somehow interferes with the fluorescence of the fluorescent protein or intensifies it, this will be evident in the control.

5. In view of the absence of any known instances in which the fluorescence activity of a reporter fluorescent protein is altered by an additional metabolite, and in view of the ready availability of a control to verify that this is the case, I believe that the presence, absence or level of fluorescence of the reporter protein is a reliable index of the activity of the promoter that has been operatively linked to the encoding sequence for said protein and thus of the effect of a test compound on that promoter.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Executed at \_\_\_\_\_, on \_\_\_\_\_ August 2007.

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ROBERT M. HOFFMAN

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Docket No.: 312762002710

enclosures:

*curriculum vitae*